

University of Groningen

Metabolic interventions in acute myocardial infarction

Horst, Johannes Cornelis Clemens van der

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version

Publisher's PDF, also known as Version of record

Publication date:
2005

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Horst, J. C. C. V. D. (2005). *Metabolic interventions in acute myocardial infarction*. s.n.

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Chapter 1

General introduction and aims of the thesis

Diagnosis and treatment of ST segment elevation myocardial infarction

College of Cardiology (ACC)⁵, and the American Heart Association (AHA)⁵ requires a typical clinical syndrome plus a rise and fall in creatine kinase-MB (CK-MB) or troponin.

Predictors of death in patients with myocardial ischemia and infarction

A number of prognostic models have been developed in populations of patients with ST segment elevation MI to determine the predictive value of several characteristics to predict outcome.⁶⁻⁹ In the multinational, observational Global Registry of Acute Coronary Events (GRACE) the value of baseline clinical and demographic characteristics on hospital mortality was predicted in an unselected population of patients with acute coronary syndrome.¹⁰ Killip class, age, blood pressure, cardiac arrest, positive enzymatic markers, serum creatinine level, ST segment deviation, and heart rate contained most of the prognostic information. Although acute coronary syndromes are usually categorized according to the presence or the absence of ST segment elevation at the time of presentation, this variable did not appear to be important for determining the risk of death after accounting for the presence of ST segment deviation. The risk of major cardiovascular complications and death is dependent on acute and pre-existing risk factors ([table 1](#)).

Table 1. High risk factors and markers of outcome

- Age
- Previous cardiovascular disease
- ST segment deviation
- Rhythm disturbances (bundle branch block, ventricular fibrillation, cardiac arrest)
- Signs of heart failure (Killip class ≥ 2)
- Glucose derangement (elevated glycosylated hemoglobin or diabetes mellitus)
- Renal dysfunction (raised serum creatinine, raised blood urea nitrogen, reduced creatinine clearance, micro-albuminuria)
- Elevated inflammatory markers (C reactive protein, interleukin-6)
- Extent of coronary artery disease on angiography (multi-vessel disease)
- Large enzymatic infarct size

General measures

The underlying principles of the treatment of ST segment elevation MI patients are to provide relief of ischemia and pain. In the presence of heart failure or shock, assisted

ventilation with positive end expiratory pressures may be required.^{4,5} Reperfusion of critically ischemic myocardium is crucial in those with acute ST elevation or (new-onset) left-bundle branch block or posterior MI. Hemodynamic support may be necessary in patients with hypotension or cardiogenic shock, i.e., patients with Killip class 4 at admission. If so indicated, this supports intra-aortic balloon pumping to stabilize the patient for PCI. Specific measures may be required to control hypertension so as to reduce myocardial wall stress, and to treat acute heart failure.

Reperfusion therapy

Early and effective reperfusion therapy is the cornerstone of treatment for acute ST segment elevation MI. Restoration of antegrade flow in the occluded artery can be achieved by PCI and/or fibrinolytic therapy. To evaluate the coronary blood flow in patients with the Thrombolysis in Myocardial Infarction (TIMI) flow is determined. The restoration of TIMI grade 3 flow, i.e., optimal flow, is achieved in approximately 9 out of 10 patients treated with PCI as compared to 5-7 out of 10 patients treated with fibrinolytic therapy.¹¹ Early restoration of antegrade flow is related to diminished enzymatic infarct size, preserved left ventricular function, prevention of recurrent infarction, and short-term as well as long-term survival benefit.

Fibrinolytic therapy

The first two large-scale, placebo-controlled, randomized trials that compared fibrinolytic therapy with placebo demonstrated dramatic benefits for streptokinase. These two trials showed that streptokinase reduced 30-day mortality rates from 13% to 10.7% ($P<0.001$)¹² and 12% to 9.2% ($P<0.001$)¹³. These results also showed the synergistic benefits of antiplatelet agents and fibrinolytic therapy, since 30-day mortality was reduced to a greater extent by the combination of aspirin and streptokinase (13.2% versus 8.0%, $P<0.001$) than by aspirin alone (11.8% versus 9.4%, $P<0.001$).^{12,13} Subsequent long-term data from both trials confirmed that the mortality benefit with streptokinase persisted for at least 10 years. Similar trials with other fibrinolytic agents have shown complementary findings, and a systematic overview of all trials randomizing more than 1000 patients to fibrinolytic therapy or placebo (total $N=58600$) reported a significant reduction in 30-day mortality with fibrinolytic therapy compared to placebo (11.5% versus 9.6%).¹⁴ Prehospital administration of fibrinolytic therapy has been proposed as a means of further reducing time to reperfusion. Several studies have analyzed the potential advantages of prehospital fibrinolytics. A recent meta-analysis ($N=6434$) that combined data from six randomized trials showed a 17% reduction in mortality with prehospital fibrinolytics versus hospital-administered fibrinolytic therapy ($P=0.03$).¹⁵ Fibrinolytic therapy is limited by various

safety and efficacy issues, such as contraindications and intracranial hemorrhage. However, until now the combination of glycoprotein IIb/IIIa receptor blockers or specific anti-thrombin (bivalirudin) and fibrinolytic therapy have not shown to improve survival, and may be associated with increased bleeding.

Primary percutaneous coronary intervention

Primary percutaneous coronary intervention (PCI) achieves reperfusion through mechanical recanalization of the infarct-related artery rather than through lysis of the coronary thrombus with fibrinolytic therapy. Dotter and Judkins were the first to propose the concept of reperfusion of the coronary artery by a catheter technique.¹⁶ In 1977, Grüntzig performed the first percutaneous balloon angioplasty.¹⁷ One year later, he and his colleagues reported that over a period of 18 months angioplasty had been used in 50 patients.¹⁸ The technique was successful in 32 patients, reducing the stenosis from a mean of 84% to 34%. Percutaneous balloon angioplasty without the use of fibrinolytic therapy for acute MI was first described by Hartzler and colleagues in 1983.¹⁹ The first stents were implanted in 1985.²⁰

The number of trials comparing primary PCI with fibrinolytic therapy has been relatively small; however, these trials found an advantage for primary PCI. The first three randomized clinical trials comparing primary PCI with various fibrinolytic regimens were published in 1993. Zijlstra and colleagues found in 142 patients that compared to streptokinase primary PCI was associated with a lower incidence of the combined end-point of recurrent infarction or angina, death, stroke, reocclusion, and heart failure (19% versus 47% $P=0.001$).²¹ Grines and colleagues found that primary PCI resulted in a lower rate of nonfatal reinfarction and death compared to tissue-type plasminogen activator (5.1% versus 12%, $P=0.02$) with a trend towards reduced overall mortality (2.6% versus 6.5%, $P=0.06$).²² Gibbons and colleagues investigated in 108 patients the effect on myocardial salvage by technetium-99m-sestamibi and could not detect any improvement with primary PCI when compared to tissue-type plasminogen activator.²³ These pioneering trials were too small to determine the magnitude of the impact of mechanical reperfusion on mortality. Subsequently, Weaver and colleagues performed a meta-analysis incorporating data from the 10 available early trials that compared primary PCI with fibrinolytic therapy. Primary PCI was associated with a significantly lower rate of 30-day mortality (4.4% versus 6.5%, $P=0.02$), as well as with a significantly lower rate of the combined end-point of death or nonfatal reinfarction (7.2% versus 11.9%, $P<0.001$). Furthermore, Zijlstra and colleagues evaluated the 5-year results in patients randomly assigned to primary PCI versus streptokinase and showed a significant reduction in mortality in the primary PCI group (13.4% versus 23.9%, $P=0.01$).²⁴

Current data are available from 23 published randomized controlled trials with 7739 patients.²⁵ Eight trials compared primary PCI to streptokinase (N=1837), and 15 primary PCI with fibrin-specific agents (N=5902). Of the 3867 patients randomly assigned to fibrinolytic therapy, most (76%, N=2939) received a fibrin-specific agent (tissue-type plasminogen activator). Stents were used in twelve and platelet glycoprotein IIb/IIIa receptor blockers in eight trials. The included trials differ in many respects, including patient sample size, type of fibrinolytic therapy, and whether the stents were used with or without platelet glycoprotein IIb/IIIa receptor blockers. Primary PCI was found to be more effective than fibrinolytic therapy in reducing short-term and long-term major adverse clinical events, including death. It was also associated with better clinical outcomes, regardless of the type of fibrinolytic agent used or whether the patient required emergent transfer to another hospital for primary PCI. Thus, primary PCI reduces mortality for patients with ST segment elevation MI even in high-risk patients. In the 'Should we emergently revascularize Occluded Coronaries for cardiogenic shock' (SHOCK) trial it was observed that at 1 year patients treated with PCI or coronary artery bypass grafting had a lower mortality than patients receiving fibrinolytic therapy (34% versus 47%, $P=0.03$). Postprocedural TIMI grade 3 flow rates in primary PCI trials have been as high as 73% to 97%, surpassing the 50% to 60% early TIMI grade 3 flow rates demonstrated with fibrinolytic therapy. Infarct-related artery reocclusion is also much less frequent after mechanical recanalization. Complications of PCI include the need for vascular repair and development of acute renal failure (approximately 3%).^{26;27}

Additional treatment

To salvage viable myocardium by re-establishing coronary blood flow with the rapid use of reperfusion strategies is an essential first step. However, reperfusion of ischemic myocardium carries with it an inherent risk. Paradoxically, the process of reperfusion itself can result in myocyte death. This phenomenon is termed reperfusion injury. Mitochondria play a key role in determining cell fate during exposure to stress. Their role during ischemia/reperfusion is particularly critical due to the conditions that promote both apoptosis by the mitochondrial pathway and necrosis by irreversible damage to mitochondria in association with mitochondrial permeability transition. Mitochondrial permeability transition is caused by the opening of permeability transition pores in the inner mitochondrial membrane, leading to matrix swelling, outer membrane rupture, release of apoptotic signaling molecules such as cytochrome *c* from the intermembrane space, and irreversible injury to the mitochondria. During ischemia, factors such as intracellular calcium accumulation, fatty acid accumulation, and reactive oxygen species progressively increase mitochondrial susceptibility to mitochondrial permeability

transition, increasing the likelihood that mitochondrial permeability transition will occur on reperfusion. Since functional cardiac recovery ultimately depends on mitochondrial recovery, cardioprotection by ischemic and pharmacological preconditioning needs to involve the prevention of mitochondrial permeability transition. Experimental studies in animals suggest that it is possible to limit the amount of myocardial damage during ischemia and the early reperfusion periods. A variety of pharmacological approaches to prevention of injury (including vasodilators, adhesion molecule blockers, and receptor blockers of complement fractions) has been investigated. One of these potential additional treatments is metabolic intervention. Drugs such as ranolazine, trimetazidine, dichloroacetate, L-carnitine²⁸ and glucose-insulin-potassium (GIK) infusion and glucagon-like peptide²⁹ have mechanisms of action distinct from traditional anti-ischemic drugs.³⁰ These agents work by shifting myocardial energy metabolism away from free fatty acids (FFA) toward glucose as a source of fuel. Since these agents are well tolerated and do not affect heart rate or blood pressure, they conceivably could supplement traditional anti-ischemic drug therapy with little risk.

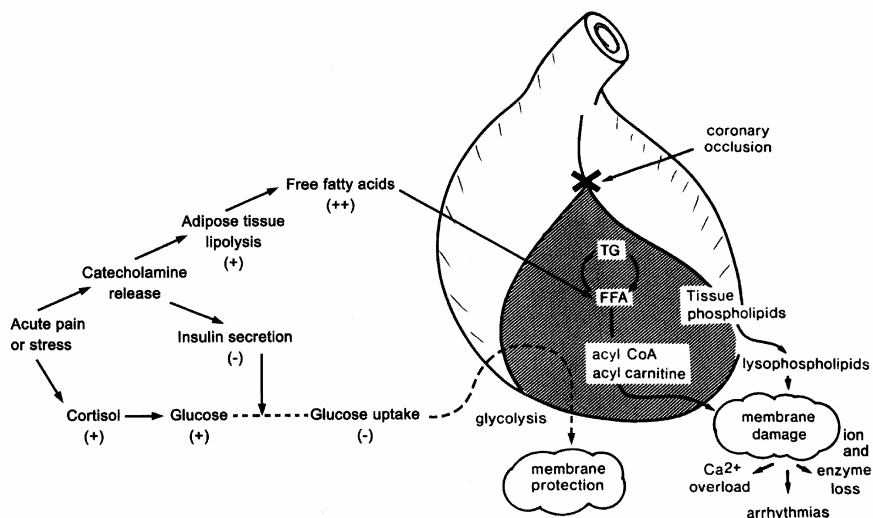
Glucose-insulin-potassium infusion in myocardial ischemia

In the timespan of almost a century, a large amount of experimental evidence has been accumulated that underlines the importance of glucose metabolism during ischemia/reperfusion of the heart. As early as 1912, Goulston suggested that treatment with glucose could be beneficial in several heart diseases.³¹ The first experimental results on the mechanical effects of insulin and glucose in the isolated heart were made by Visscher and Muller in 1926.³² In 1935, Evans and colleagues showed that in the ischemic myocardium the uptake of glucose is increased.³³ Almost 30 years later, Sodi-Pallares and colleagues suggested that metabolic interference during myocardial ischemia with GIK infusion decreased electrocardiographic signs of ischemia.³⁴ They also showed that GIK infusion resulted in a lower occurrence of arrhythmias.³⁴ They attributed this effect mainly to the influx of potassium in ischemic cardiomyocytes.³⁵ In order to further stimulate potassium transport into the cell, insulin was administered.³⁶ Consequently, the rise of intercellular calcium is curtailed by the influx of potassium and so the incidence of arrhythmias is reduced.³⁷⁻⁴⁰ However, systemic infusion of insulin stimulates the uptake of glucose in many celltypes⁴¹, which may result in hypoglycemic episodes.⁴² Consequently, it is not possible to administer potassium and insulin in high concentrations without adding glucose. Interventions in the glucose metabolism in the clinical arena, whether or not used to correct acute hyperglycemia, encompass three potentially effective elements: glucose, insulin and potassium.

Basic mechanism of GIK protection

Ischemia induces many changes in the heart's metabolism, including shifts from aerobic fatty acid metabolism to anaerobic glycolysis, which provides energy for critical myocardial cellular function ([figure 1](#)).⁴³⁻⁴⁵

Figure 1. The main changes that occur in peripheral and myocardial metabolism during the development of acute myocardial ischemia. [adapted from Oliver MF. Am J Med 2002;112:305-311]



CoA = coenzyme A; FFA = free fatty acid; TG = triglyceride.

During most clinical ischemic syndromes, including acute MI, residual or collateral blood flow usually provides at least 10% of the normal level of perfusion to a significant portion of the ischemic myocardium. This small amount of perfusion provides such a level of oxygen delivery that oxidative ATP synthesis from both glucose and free fatty acids greatly exceeds ATP synthesis from anaerobic glycolysis.^{46;47} Thus, a mixture of aerobic and anaerobic metabolism occurs. With progressively severe ischemia, anaerobic glycolysis becomes a progressively more important source of energy for a limited amount of ATP, which may or may not suffice to support the most essential cellular functions. Glycogen is rapidly mobilized during ischemia, and reduced glycogen concentrations impair force development, calcium release, and contractile function.⁴⁸ Key intermediates of the Krebs cycle are also depleted, which may impair energy transfer.⁴⁹ The ischemia-mediated increase in glucose utilization is characterized by enhanced rates of exogenous glucose uptake in vivo, which requires greater rates of transport across the

plasma membrane.^{50;51} Of the seven reported members of the facilitative glucose transporter family, GLUT-4 and GLUT-1 are the primary forms expressed in adult mammalian heart muscle.⁵² During low-flow ischemia the expression of GLUT-4 is doubled.⁵³ Insulin increases the translocation of GLUT-4 via a pathway mediated by phosphatidylinositol 3-kinase (PI3-K). During ischemia and hypoxia GLUT-4 translocation is stimulated through a PI3-K-independent pathway. AMP-activated protein kinase plays a role in the translocation during ischemia.⁵⁴

Table 2. Mechanisms of GIK infusion during myocardial ischemia⁶²⁻⁶⁴

- The yield of moles of ATP per mole of oxygen consumed is 11 percent higher for glucose than for FFA oxidation
- Anti FFA effects
 - Decrease of circulating FFA levels and myocardial FFA uptake
 - Increased esterification of intracellular FFA by increasing the supply of alpha-glycerophosphate
- Increased rate of ATP synthesis via anaerobic glycolysis with consequent beneficial effects
 - Increased concentrations of phosphocreatine and ATP
 - Blunting of an increase in inorganic phosphate and ADP concentrations
 - Increased free energy yield from ATP hydrolysis
- Increased myocardial glycogen
- Improved sodium and calcium homeostasis
- Increased tolerance to rises in intracellular calcium
- Replenishment of citric acid cycle intermediates by anaplerosis
- Increase of glucose and decrease of FFA oxidation during reperfusion
- Activation of cell survival signalling pathways such as Akt

Opie proposed the glucose hypothesis: the enhanced uptake and metabolism of glucose delays cellular damage.^{55;56} Glucose utilization during ischemia prevents the breakdown of glycogen stores and leads to increased net intramyocardial glycogen synthesis, thereby limiting enzymatic infarct size and contracture.^{47;57} Two studies showed that infusion of GIK in isolated hearts with regional ischemia resulted in decreased infarct size, increased high-energy phosphate levels, and improved ventricular function.^{58;59} Acute MI patients treated with GIK also showed better stress tolerance and ischemic threshold improvement, analyzed with technetium-99m-tetrofosmin-gated SPECT.⁶⁰ The improved energetic profile results in improved systolic and diastolic function during ischemia and reperfusion, as well as coronary vasodilatation.⁴⁷ Also, glucose uptake has been shown to reduce hypoxia-induced apoptosis in cultured neonatal rat cardiac myocytes.⁶¹ The

observed benefits of GIK infusion have been attributed to a number of mechanisms, which are summarized in [table 2](#) and in part discussed.

Glucose

The potential positive effects of glucose are based on the fact that glucose is a source of energy for cells.⁶⁵ The uptake of glucose into the cell is influenced by insulin, although there is also an insulin-independent transport of glucose.⁶⁶ It has been observed that AMP-activated protein kinase is responsible for activation of glucose uptake and glycolysis during low-flow ischemia.⁶⁷ During MI, low-flow perfusion of the ischemic area is often present, making the administration glucose useful.⁴⁸ In an experimental study it was observed that a high glucose concentration stimulated translocation of GLUT-4.⁶⁸ It was already known that the combination of glucose and insulin is more effective than either one alone in stimulating glycolysis under ischemic conditions.⁴⁷

Administering glucose can prevent insulin-induced hypoglycemia. When the hypoglycemic episodes persist or when they are severe (<2.7 mmol/L), convulsions, brain damage and even brain death may occur.⁶⁹ Hypoglycemia is also related to myocardial ischemia.⁷⁰ It has been shown that the prevention of hypoglycemia can prevent an increase in enzymatic infarct size.⁷¹ When hypoglycemia occurs, the contraregulating hormones are activated and result in an increased release of glucose.⁷² Increased glucose release requires, in particular, an increase in glucagon and adrenaline. During MI the levels of glucagon, adrenaline and aldosterone among others are already elevated.

Insulin

The potential positive effects of insulin during stress situations are multifarious.^{73;74} First, insulin is involved in the uptake of glucose in tissues, including the myocardium, mainly through GLUT-4 and partly through GLUT-1.⁷⁵ However, the exact amount of uptake during ischemia is disputable.⁷⁶ Besides the stimulation of glucose uptake and the stimulation of glycogen synthesis, insulin is also involved in gene transcription, expression of various metabolic enzymes, the activation of various pathways with mitogenic activity, and even fatty acid uptake. The insulin receptor substrate 1 has an important role in realizing this pleiotrope.⁷⁷ Both insulin-like growth factor (IGF) 1 and insulin inhibit postischemic apoptosis, energetic failure and damage to cardiac tissue, in vitro and in animals, possibly through reduced oxidative stress.^{78;79} Insulin increases the bio-availability of IGF1 and suppresses hepatic synthesis of IGF1-binding protein, which binds and limits free-circulating IGF1.^{80;81}

Insulin stimulates protein synthesis in skeletal muscles and inhibits intracellular protein breakdown in cardiac tissue.⁸²⁻⁸⁴ The preservation of myocardial cells by inhibiting apoptosis and reduced destruction of proteins could be the reason that contractility is

preserved.⁸⁵ An additional factor is that insulin potentiates ischemic preconditioning; however, this has not been proven irrefutably in clinical trials.^{86;87}

Insulin has an anti-inflammatory effect that is caused by a reduction in oxidative stress.⁸⁸ First, insulin reduces the pro-inflammatory effects of hyperglycemia. Insulin suppresses the production of tumor necrosis factor α in macrophages, leucocytes and endothelium.⁸⁹ Furthermore, insulin blocks the upregulation of the endothelial cell adhesion molecule induced by hyperglycemia.^{90;91} Also, insulin inhibits macrophage-inhibitory factor, and potentiates endothelial nitric oxide synthase and endothelin release.⁹² In a clinical study it appeared that the oxidative stress that occurs in myocardial ischemia and during reperfusion by primary PCI could not be suppressed by insulin.⁹³

Insulin is shown to influence the adhesion of leucocytes and blood platelets during an acute MI.⁹⁴ A study with 48 patients with type 2 diabetes mellitus showed that intensive treatment with insulin during an acute ischemic event (i.e., acute MI or unstable angina pectoris) improves the fibrinolytic profile.⁹⁵ The administration of insulin with the aid of an algorithm led to lower mean blood-glucose values (6.9 mmol/L versus 11.4 mmol/L) and to lower concentrations of tissue plasminogen activator, plasminogen activator inhibitor-1 and fibrinogen.

Insulin has vasodilating capacities in blood vessels of muscle tissue.^{96;97} Vasodilatation during myocardial ischemia has been observed both in patients with and without diabetes mellitus.⁹⁷⁻⁹⁹ This is advantageous, since it opens up the blood vessels in the myocardium, enabling more glucose to reach the cells and preventing the accumulation of metabolites that are toxic and cause mitochondrial damage and alterations in membrane ion channels.^{98;100} Vasodilatation occurs, among others, by stimulating the production of nitric oxide in the endothelium and by antagonizing endothelin, a potent vasoconstrictor.^{101;102} Even a small increase in myocardial blood flow can significantly reduce myocardial ischemia.¹⁰³

Conversely, administering insulin can potentially lead to an adverse reaction.¹⁰⁴ It might lead to enhanced polarisability of the cell membrane, stimulation of the sympathetic nervous system, and inhibition of the parasympathic nervous system. In contrast to the above-mentioned results, it was also found that insulin induced oxidative stress.¹⁰⁵ The effect of insulin on nuclear factor- κ B (NF- κ B) remains unclear.^{88;106} In an experimental setting insulin in high amounts has inhibitory effects on intermediates involved in the activation by platelet-derived growth factor.¹⁰⁷

Potassium

It appears that hypokaliemia during stress situations is disadvantageous.^{108;109} Hypokaliemia frequently occurs in trauma patients and has been associated with a worse score on the Glasgow Coma Score (GCS).¹¹⁰ Moreover, hypokaliemia has been associated

with muscle necrosis and paralysis. In patients with myocardial ischemia, hypokaliemia increases the risk of ventricular arrhythmias and acute cardiac arrest.¹¹¹ Restoring the potassium concentration in the cell and in serum may be accompanied by a decrease in the incidence and severity of arrhythmias.¹¹² However, when the effect of GIK infusion on QT-time was analyzed, no effect was found.¹¹³ Consequently, administration of potassium in stress situations is mandatory to patients who present with hypokaliemia as well as to patients treated with insulin in order to prevent hypokaliemia. Moreover, hypokaliemia appears to suppress the secretion of insulin, and in this way stimulates a (continued) state of hyperglycemia.¹¹⁴

This thesis

This thesis is a new branch on the large tree of studies on optimal therapeutic strategy for and understanding of ST segment elevation MI. In 1989, the Zwolle Myocardial Infarction Study Group performed its first study of comparing PCI with streptokinase. Thereafter studies on the effect of primary PCI, stenting, intra-aortic balloon counterpulsation, prehospital treatment with heparin and glycoprotein IIb/IIIa receptor blockers have been reported. Over the last years more research has been done to investigate the causative mechanisms behind favorable and unfavorable outcome after treatment with primary PCI. Currently, special emphasis is given to the effect of glucose derangements and patients with diabetes mellitus. The concept to add a metabolic intervention to the treatment strategy of primary PCI was formulated in 1997.

The purpose of this thesis is to investigate the effect of metabolic interventions and disturbances on the clinical outcome and myocardial function in ST segment elevation MI patients. Therefore, we have investigated whether GIK infusion in adjunction to primary PCI reduces 30-day ([Chapter 2.1](#)) and 3-year mortality ([Chapter 2.6](#)) in ST segment elevation MI patients. We also investigated the effects of GIK infusion on myocardial infarct size ([Chapter 2.2](#)), left ventricular function ([Chapters 2.2 and 2.3](#)) and ST segment elevation resolution ([Chapter 2.4](#)). Furthermore, we investigated the metabolic derangements induced by GIK infusion, and the impact of metabolic derangements on clinical outcome ([Chapter 2.5](#)). With the results of the GIPS we performed a new analysis on all available results of GIK infusion on 30-day mortality ([Chapter 3](#)).

In the second part of this thesis we report our studies on the relation between hyperglycemia and outcome. Based on a large body of evidence it is known that hyperglycemia at admission is related to mortality. We were able to analyze the effect of admission hyperglycemia on myocardial function ([Chapter 4.1](#)). The predictive value of

admission glucose is not strong and we hypothesized that persistent hyperglycemia in both critically ill patients admitted to a Coronary Care Unit ([Chapter 5.1](#)) and an Intensive Care Unit ([Chapter 5.2 and 5.3](#)) could be a better determinant for unfavorable outcome. Based on the results found in the above-mentioned studies, we wrote the protocol of the GIPS-2 a multi-center trial on the effect of GIK infusion in ST segment elevation MI patients without signs of heart-failure and eligible for reperfusion therapy ([Chapter 6](#)). Finally, this thesis purposes to give future directions for the implementation of metabolic interventions in critically ill patients ([Chapter 7](#)).

References

1. DeWood MA, Spores J, Notske R et al. Prevalence of total coronary occlusion during the early hours of transmural myocardial infarction. *N Engl J Med* 1980;303:897-902.
2. Obrastzow WP, Straschesko ND. [Zur kenntnis der thrombose der koronararterien des herzens]. *Z Klin Med* 1912;71:116-32.
3. Herrick JB. Clinical features of sudden obstruction of the coronary arteries. *J Am Med Assoc* 1912;59:2015-20.
4. Van de Werf F, Ardissino D, Betriu A et al. Management of acute myocardial infarction in patients presenting with ST segment elevation. The Task Force on the Management of Acute Myocardial Infarction of the European Society of Cardiology. *Eur Heart J* 2003;24:28-66.
5. Ryan TJ, Antman EM, Brooks NH et al. 1999 update: ACC/AHA Guidelines for the Management of Patients With Acute Myocardial Infarction: Executive Summary and Recommendations: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction). *Circulation* 1999;100:1016-30.
6. Lee KL, Woodlief LH, Topol EJ et al. Predictors of 30-day mortality in the era of reperfusion for acute myocardial infarction. Results from an international trial of 41,021 patients. GUSTO-I Investigators. *Circulation* 1995;91:1659-68.
7. Morrow DA, Antman EM, Charlesworth A et al. TIMI risk score for ST-elevation myocardial infarction: A convenient, bedside, clinical score for risk assessment at presentation: An intravenous nPA for treatment of infarcting myocardium early II trial substudy. *Circulation* 2000;102:2031-37.
8. Morrow DA, Antman EM, Giugliano RP et al. A simple risk index for rapid initial triage of patients with ST-elevation myocardial infarction: an InTIME II substudy. *Lancet* 2001;358:1571-75.
9. Krumholz HM, Chen J, Wang Y, Radford MJ, Chen YT, Marciniak TA. Comparing AMI mortality among hospitals in patients 65 years of age and older: evaluating methods of risk adjustment. *Circulation* 1999;99:2986-92.
10. Eagle KA, Lim MJ, Dabbous OH et al. A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6-month postdischarge death in an international registry. *JAMA* 2004;291:2727-33.

11. de Boer MJ, Reiber JH, Suryapranata H, van den Brand MJ, Hoorntje JC, Zijlstra F. Angiographic findings and catheterization laboratory events in patients with primary coronary angioplasty or streptokinase therapy for acute myocardial infarction. *Eur Heart J* 1995;16:1347-55.
12. Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI) *Lancet* 1986;1:397-402.
13. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group *Lancet* 1988;2:349-60.
14. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group *Lancet* 1994;343:311-22.
15. Morrison LJ, Verbeek PR, McDonald AC, Sawadsky BV, Cook DJ. Mortality and prehospital thrombolysis for acute myocardial infarction: A meta-analysis. *JAMA* 2000;283:2686-92.
16. Dotter CT, Judkins MP. Transluminal treatment of arteriosclerotic obstruction. Description of a new technic and a preliminary report of its application. *Circulation* 1964;30:654-70.
17. Gruntzig A. Transluminal dilatation of coronary-artery stenosis. *Lancet* 1978;1:263.
18. Gruntzig AR, Senning A, Siegenthaler WE. Nonoperative dilatation of coronary-artery stenosis: percutaneous transluminal coronary angioplasty. *N Engl J Med* 1979;301:61-68.
19. Hartzler GO, Rutherford BD, McConahay DR et al. Percutaneous transluminal coronary angioplasty with and without thrombolytic therapy for treatment of acute myocardial infarction. *Am Heart J* 1983;106:965-73.
20. Sigwart U, Puel J, Mirkovitch V, Joffe F, Kappenberger L. Intravascular stents to prevent occlusion and restenosis after transluminal angioplasty. *N Engl J Med* 1987;316:701-6.
21. Zijlstra F, de Boer MJ, Hoorntje JC, Reiffers S, Reiber JH, Suryapranata H. A comparison of immediate coronary angioplasty with intravenous streptokinase in acute myocardial infarction. *N Engl J Med* 1993;328:680-684.
22. Grines CL, Browne KF, Marco J et al. A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. The Primary Angioplasty in Myocardial Infarction Study Group. *N Engl J Med* 1993;328:673-79.
23. Gibbons RJ, Holmes DR, Reeder GS, Bailey KR, Hopfenspirger MR, Gersh BJ. Immediate angioplasty compared with the administration of a thrombolytic agent followed by conservative treatment for myocardial infarction. The Mayo Coronary Care Unit and Catheterization Laboratory Groups. *N Engl J Med* 1993;328:685-91.
24. Zijlstra F, Hoorntje JC, de Boer MJ et al. Long-term benefit of primary angioplasty as compared with thrombolytic therapy for acute myocardial infarction. *N Engl J Med* 1999;341:1413-19.
25. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet* 2003;361:13-20.

26. Lindsay J, Apple S, Pinnow EE et al. Percutaneous coronary intervention-associated nephropathy foreshadows increased risk of late adverse events in patients with normal baseline serum creatinine. *Catheter Cardiovasc Interv* 2003;59:338-43.
27. Rihal CS, Textor SC, Grill DE et al. Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. *Circulation* 2002;105:2259-64.
28. Wolff AA, Rotmensch HH, Stanley WC, Ferrari R. Metabolic approaches to the treatment of ischemic heart disease: the clinicians' perspective. *Heart Fail Rev* 2002;7:187-203.
29. Huisamen B, Genade S, Lochner A. Glucagon-like peptide-1 (GLP-1) protects the heart against ischaemia by activating glycolysis. *Cardiovasc J S Afr* 2004;15:S15.
30. Opie LH. The metabolic vicious cycle in heart failure. *Lancet* 2004;364:1733-34.
31. Goulston A. West Indian cane sugar in treatment of certain forms of heart diseases. *British Medical Journal* 1912;2:693-95.
32. Visscher MB, Muller EA. The influence of insulin upon the mammalian heart. *J Physiol* 1926;62:341-48.
33. Evans CL, Grande F, Musu FJ. The glucose and lactate consumption of the dog's heart. *Quart J Exptl Physiol* 1935;24:347-52.
34. Sodi-Pallares D, Testelli MR, Fishleder BL et al. Effects of an intravenous infusion of a potassium-glucose-insulin solution on the electrocardiographic signs of myocardial infarction. A preliminary clinical report. *Am J Cardiol* 1962;9:166-81.
35. Sodi-Pallares D, Bisteni A, Medrano GA, Testelli MR, de Micheli A. The polarizing treatment of acute myocardial infarction. Possibility of its use in other cardiovascular conditions. *Dis Chest* 1963;43:424-32.
36. Zierler K, Rogus EM, Scherer RW, Wu FS. Insulin action on membrane potential and glucose uptake: effects of high potassium. *Am J Physiol* 1985;249:E17-E25.
37. Aulbach F, Simm A, Maier S et al. Insulin stimulates the L-type Ca²⁺ current in rat cardiac myocytes. *Cardiovasc Res* 1999;42:113-20.
38. Danielson KS, DeWeese JA, Mahoney EB. Evaluation of dextrose, insulin, and potassium on ventricular irritability in acute myocardial infarction. *J Thorac Cardiovasc Surg* 1970;60:653-60.
39. Harris AS, Toth LA, Tan EH. Arrhythmic and antiarrhythmic effects of sodium, potassium, and calcium salts and of glucose injected into coronary arteries of infarcted and normal hearts. *Circ Res* 1958;6:570-579.
40. Schonekess BO, Brindley PG, Lopaschuk GD. Calcium regulation of glycolysis, glucose oxidation, and fatty acid oxidation in the aerobic and ischemic heart. *Can J Physiol Pharmacol* 1995;73:1632-40.
41. Ferrannini E, Santoro D, Bonadonna R, Natali A, Parodi O, Camici PG. Metabolic and hemodynamic effects of insulin on human hearts. *Am J Physiol* 1993;264:E308-E315.
42. Sands MJ, Jr., McDonough MT, Neubauer SJ, Lemole GM, Spann JF. Hypoglycemia complicating the use of solution of glucose, insulin and potassium. *Chest* 1975;67:363-65.
43. Apstein CS. Increased glycolytic substrate protection improves ischemic cardiac dysfunction and reduces injury. *Am Heart J* 2000;139:S107-S114.
44. Opie LH. Metabolic response during impending myocardial infarction. I. Relevance of studies of glucose and fatty acid metabolism in animals. *Circulation* 1972;45:483-90.

45. Whitmer JT, Idell-Wenger JA, Rovetto MJ, Neely JR. Control of fatty acid metabolism in ischemic and hypoxic hearts. *J Biol Chem* 1978;253:4305-9.
46. Cave AC, Ingwall JS, Friedrich J et al. ATP synthesis during low-flow ischemia: influence of increased glycolytic substrate. *Circulation* 2000;101:2090-2096.
47. Eberli FR, Weinberg EO, Grice WN, Horowitz GL, Apstein CS. Protective effect of increased glycolytic substrate against systolic and diastolic dysfunction and increased coronary resistance from prolonged global underperfusion and reperfusion in isolated rabbit hearts perfused with erythrocyte suspensions. *Circ Res* 1991;68:466-81.
48. Chin ER, Allen DG. Effects of reduced muscle glycogen concentration on force, Ca²⁺ release and contractile protein function in intact mouse skeletal muscle. *J Physiol* 1997;498 (Pt 1):17-29.
49. Taegtmeier H, Goodwin GW, Doenst T, Frazier OH. Substrate metabolism as a determinant for postischemic functional recovery of the heart. *Am J Cardiol* 1997;80:3A-10A.
50. Schwaiger M, Neese RA, Araujo L et al. Sustained nonoxidative glucose utilization and depletion of glycogen in reperfused canine myocardium. *J Am Coll Cardiol* 1989;13:745-54.
51. Guth BD, Wisneski JA, Neese RA et al. Myocardial lactate release during ischemia in swine. Relation to regional blood flow. *Circulation* 1990;81:1948-58.
52. Stephens JM, Pilch PF. The metabolic regulation and vesicular transport of GLUT4, the major insulin-responsive glucose transporter. *Endocr Rev* 1995;16:529-46.
53. Young LH, Renfu Y, Russell R et al. Low-flow ischemia leads to translocation of canine heart GLUT-4 and GLUT-1 glucose transporters to the sarcolemma in vivo. *Circulation* 1997;95:415-22.
54. Russell RR, III, Bergeron R, Shulman GI, Young LH. Translocation of myocardial GLUT-4 and increased glucose uptake through activation of AMPK by AICAR. *Am J Physiol* 1999;277:H643-H649.
55. Opie LH. Hypothesis: Glycolytic rates control cell viability in ischemia. *J Appl Cardiol* 1988;3:407-14.
56. Opie LH. The glucose hypothesis: its relation to acute myocardial ischemia. *J Mol Cell Cardiol* 1970;1:107-15.
57. Owen P, Dennis S, Opie LH. Glucose flux rate regulates onset of ischemic contracture in globally underperfused rat hearts. *Circ Res* 1990;66:344-54.
58. Heng MK, Norris RM, Singh BN, Barratt-Boyes C. Effects of glucose and glucose-insulin-potassium on haemodynamics and enzyme release after acute myocardial infarction. *Br Heart J* 1977;39:748-57.
59. Maroko PR, Libby P, Sobel BE et al. Effect of glucose-insulin-potassium infusion on myocardial infarction following experimental coronary artery occlusion. *Circulation* 1972;45:1160-1175.
60. Marano L, Bestetti A, Lomuscio A et al. Effects of infusion of glucose-insulin-potassium on myocardial function after a recent myocardial infarction. *Acta Cardiol* 2000;55:9-15.
61. Malhotra R, Brosius FC, III. Glucose uptake and glycolysis reduce hypoxia-induced apoptosis in cultured neonatal rat cardiac myocytes. *J Biol Chem* 1999;274:12567-75.
62. Apstein CS, Gravino FN, Haudenschield CC. Determinants of a protective effect of glucose and insulin on the ischemic myocardium. Effects on contractile function, diastolic

- compliance, metabolism, and ultrastructure during ischemia and reperfusion. *Circ Res* 1983;52:515-26.
63. Apstein CS, Taegtmeier H. Glucose-insulin-potassium in acute myocardial infarction: the time has come for a large, prospective trial. *Circulation* 1997;96:1074-77.
 64. Apstein CS. The benefits of glucose-insulin-potassium for acute myocardial infarction (and some concerns). *J Am Coll Cardiol* 2003;42:792-95.
 65. Gerich JE. Control of glycaemia. *Baillieres Clin Endocrinol Metab* 1993;7:551-86.
 66. Mizock BA. Alterations in fuel metabolism in critical illness: hyperglycaemia. *Best Pract Res Clin Endocrinol Metab* 2001;15:533-51.
 67. Russell RR, III, Li J, Coven DL et al. AMP-activated protein kinase mediates ischemic glucose uptake and prevents postischemic cardiac dysfunction, apoptosis, and injury. *J Clin Invest* 2004;114:495-503.
 68. Ramasamy R, Payne JA, Whang J, Bergmann SR, Schaefer S. Protection of ischemic myocardium in diabetics by inhibition of electroneutral Na⁺-K⁺-2Cl⁻ cotransporter. *Am J Physiol Heart Circ Physiol* 2001;281:H515-H522.
 69. Mitrakou A, Ryan C, Veneman T et al. Hierarchy of glycemic thresholds for counterregulatory hormone secretion, symptoms, and cerebral dysfunction. *Am J Physiol* 1991;260:E67-E74.
 70. Desouza CV, Murthy SN, Diez J et al. Differential effects of peroxisome proliferator activator receptor- α and γ ligands on intimal hyperplasia after balloon catheter-induced vascular injury in Zucker rats. *J Cardiovasc Pharmacol Ther* 2003;8:297-305.
 71. Libby P, Maroko PR, Braunwald E. The effect of hypoglycemia on myocardial ischemic injury during acute experimental coronary artery occlusion. *Circulation* 1975;51:621-26.
 72. Rizza RA, Cryer PE, Gerich JE. Role of glucagon, catecholamines, and growth hormone in human glucose counterregulation. Effects of somatostatin and combined α - and β -adrenergic blockade on plasma glucose recovery and glucose flux rates after insulin-induced hypoglycemia. *J Clin Invest* 1979;64:62-71.
 73. Das UN. Insulin: an endogenous cardioprotector. *Curr Opin Crit Care* 2003;9:375-83.
 74. Groeneveld AB, Beishuizen A, Visser FC. Insulin: a wonder drug in the critically ill? *Crit Care* 2002;6:102-5.
 75. McNulty PH, Jacob R, Deckelbaum LI, Young LH. Effect of hyperinsulinemia on myocardial amino acid uptake in patients with coronary artery disease. *Metabolism* 2000;49:1365-69.
 76. Liedtke AJ, Hughes HC, Neely JR. Effects of excess glucose and insulin on glycolytic metabolism during experimental myocardial ischemia. *Am J Cardiol* 1976;38:17-27.
 77. Sun XJ, Wang LM, Zhang Y et al. Role of IRS-2 in insulin and cytokine signalling. *Nature* 1995;377:173-77.
 78. Aikawa R, Nawano M, Gu Y et al. Insulin prevents cardiomyocytes from oxidative stress-induced apoptosis through activation of PI3 kinase/Akt. *Circulation* 2000;102:2873-79.
 79. Jonassen AK, Brar BK, Mjos OD, Sack MN, Latchman DS, Yellon DM. Insulin administered at reoxygenation exerts a cardioprotective effect in myocytes by a possible anti-apoptotic mechanism. *J Mol Cell Cardiol* 2000;32:757-64.

80. Nygren J, Carlsson-Skwirut C, Brismar K, Thorell A, Ljungqvist O, Bang P. Insulin infusion increases levels of free IGF-I and IGFBP-3 proteolytic activity in patients after surgery. *Am J Physiol Endocrinol Metab* 2001;281:E736-E741.
81. Timmins AC, Cotterill AM, Hughes SC et al. Critical illness is associated with low circulating concentrations of insulin-like growth factors-I and -II, alterations in insulin-like growth factor binding proteins, and induction of an insulin-like growth factor binding protein 3 protease. *Crit Care Med* 1996;24:1460-1466.
82. Madibally SV, Solomon V, Mitchell RN, Van De WL, Yarmush ML, Toner M. Influence of insulin therapy on burn wound healing in rats. *J Surg Res* 2003;109:92-100.
83. Solomon V, Madihally S, Mitchell RN, Yarmush M, Toner M. Antiproteolytic action of insulin in burn-injured rats. *J Surg Res* 2002;105:234-42.
84. Young LH, Dahl DM, Rauner D, Barrett EJ. Physiological hyperinsulinemia inhibits myocardial protein degradation in vivo in the canine heart. *Circ Res* 1992;71:393-400.
85. Whitlow PL, Rogers WJ, Smith LR et al. Enhancement of left ventricular function by glucose-insulin-potassium infusion in acute myocardial infarction. *Am J Cardiol* 1982;49:811-20.
86. Kersten JR, Schmelting TJ, Orth KG, Pagel PS, Warltier DC. Acute hyperglycemia abolishes ischemic preconditioning in vivo. *Am J Physiol* 1998;275:H721-H725.
87. Kersten JR, Montgomery MW, Ghassemi T et al. Diabetes and hyperglycemia impair activation of mitochondrial K(ATP) channels. *Am J Physiol Heart Circ Physiol* 2001;280:H1744-H1750.
88. Dandona P, Aljada A, Mohanty P et al. Insulin inhibits intranuclear nuclear factor kappaB and stimulates IkappaB in mononuclear cells in obese subjects: evidence for an anti-inflammatory effect? *J Clin Endocrinol Metab* 2001;86:3257-65.
89. Rosenzweig T, Braiman L, Bak A, Alt A, Kuroki T, Sampson SR. Differential effects of tumor necrosis factor-alpha on protein kinase C isoforms alpha and delta mediate inhibition of insulin receptor signaling. *Diabetes* 2002;51:1921-30.
90. Booth G, Stalker TJ, Lefer AM, Scalia R. Elevated ambient glucose induces acute inflammatory events in the microvasculature: effects of insulin. *Am J Physiol Endocrinol Metab* 2001;280:E848-E856.
91. Booth G, Stalker TJ, Lefer AM, Scalia R. Mechanisms of amelioration of glucose-induced endothelial dysfunction following inhibition of protein kinase C in vivo. *Diabetes* 2002;51:1556-64.
92. Kuboki K, Jiang ZY, Takahara N et al. Regulation of endothelial constitutive nitric oxide synthase gene expression in endothelial cells and in vivo : a specific vascular action of insulin. *Circulation* 2000;101:676-81.
93. Diaz-Araya G, Nettle D, Castro P et al. Oxidative stress after reperfusion with primary coronary angioplasty: lack of effect of glucose-insulin-potassium infusion. *Crit Care Med* 2002;30:417-21.
94. Bertuglia S, Giusti A, Fedele S, Picano E. Glucose-insulin-potassium treatment in combination with dipyridamole inhibits ischaemia-reperfusion-induced damage. *Diabetologia* 2001;44:2165-70.

95. Melidonis A, Stefanidis A, Tournis S et al. The role of strict metabolic control by insulin infusion on fibrinolytic profile during an acute coronary event in diabetic patients. *Clin Cardiol* 2000;23:160-164.
96. Legtenberg RJ, Houston RJ, Oeseburg B, Smits P. Physiological insulin concentrations protect against ischemia-induced loss of cardiac function in rats. *Comp Biochem Physiol A Mol Integr Physiol* 2002;132:161-67.
97. McNulty PH, Pfau S, Deckelbaum LI. Effect of plasma insulin level on myocardial blood flow and its mechanism of action. *Am J Cardiol* 2000;85:161-65.
98. Rogers WJ, Russell RO, Jr., McDaniel HG, Rackley CE. Acute effects of glucose-insulin-potassium infusion on myocardial substrates, coronary blood flow and oxygen consumption in man. *Am J Cardiol* 1977;40:421-28.
99. Sundell J, Knuuti J. Insulin and myocardial blood flow. *Cardiovasc Res* 2003;57:312-19.
100. Nava P, Carbo R, Guarner V. Coronary and femoral arterial contraction with high glucose, insulin, and glucose-insulin-potassium solution: effects of hypoxia. *Heart Vessels* 2002;16:57-63.
101. Nava P, Collados MT, Masso F, Guarner V. Endothelin mediation of insulin and glucose-induced changes in vascular contractility. *Hypertension* 1997;30:825-29.
102. Verma S, Yao L, Stewart DJ, Dumont AS, Anderson TJ, McNeill JH. Endothelin antagonism uncovers insulin-mediated vasorelaxation in vitro and in vivo. *Hypertension* 2001;37:328-33.
103. Apstein CS, Deckelbaum L, Mueller M, Hagopian L, Hood WB, Jr. Graded global ischemia and reperfusion. Cardiac function and lactate metabolism. *Circulation* 1977;55:864-72.
104. Quinones-Galvan A, Ferrannini E. Metabolic effects of glucose-insulin infusions: myocardium and whole body. *Curr Opin Clin Nutr Metab Care* 2001;4:157-63.
105. Kashiwagi A, Shinozaki K, Nishio Y et al. Endothelium-specific activation of NAD(P)H oxidase in aortas of exogenously hyperinsulinemic rats. *Am J Physiol* 1999;277:E976-E983.
106. Golovchenko I, Goalstone ML, Watson P, Brownlee M, Draznin B. Hyperinsulinemia enhances transcriptional activity of nuclear factor-kappaB induced by angiotensin II, hyperglycemia, and advanced glycosylation end products in vascular smooth muscle cells. *Circ Res* 2000;87:746-52.
107. Goalstone ML, Natarajan R, Standley PR et al. Insulin potentiates platelet-derived growth factor action in vascular smooth muscle cells. *Endocrinology* 1998;139:4067-72.
108. He FJ, MacGregor GA. Fortnightly review: Beneficial effects of potassium. *BMJ* 2001;323:497-501.
109. Gennari FJ. Disorders of potassium homeostasis. Hypokalemia and hyperkalemia. *Crit Care Clin* 2002;18:273-88, vi.
110. Beal AL, Scheltema KE, Beilman GJ, Deuser WE. Hypokalemia following trauma. *Shock* 2002;18:107-10.
111. Schulman M, Narins RG. Hypokalemia and cardiovascular disease. *Am J Cardiol* 1990;65:4E-9E.
112. Schwartz AB. Potassium-related cardiac arrhythmias and their treatment. *Angiology* 1978;29:194-205.

Introduction

Treatment strategies for acute ST segment elevation myocardial infarction (MI) have evolved over the last 25 years. In the 1950s and 1960s, it was debated whether coronary thrombosis was the cause or the consequence of ST segment elevation MI. In the 1960s and 1970s, treatment of ST segment elevation MI patients consisted of bed rest for up to a month. Mortality was reduced with the emergence of Coronary Care Units and treatment of the arrhythmias. Landmark studies by DeWood in the early 1980s showed that occlusion of the coronary artery was the critical event leading to ST segment elevation MI.¹ Reperfusion therapy became the cornerstone of acute treatment for ST segment elevation MI. Preferentially, acute coronary reperfusion is nowadays accomplished (1) mechanically by primary percutaneous coronary intervention (PCI), previously called primary transluminal coronary angioplasty (PTCA) with or without stenting or (2) pharmacologically with intravenous fibrinolytic therapy. Recent evidence suggests that apart from improved PCI techniques, adjunctive use of platelet glycoprotein IIb/IIIa receptor blockers and metabolic interventions, such as glucose-insulin-potassium (GIK) infusion may enhance procedural success and improve clinical outcome. Together these developments have stimulated renewed efforts to determine the optimal therapeutic strategy for patients with ST segment elevation MI.

Pathophysiology

The first papers on the clinical diagnosis of MI date from the early 20th century. Obrastzow and Strachescenko in 1910 and Herrick in 1912 described the features of a sudden obstruction of a coronary artery.^{2,3}

Myocardial infarction is the consequence of disruption, fissuring or hemorrhage of a vulnerable coronary artery plaque, complicated by various degrees of intraluminal thrombosis, embolization, and subtotal or total obstruction to perfusion. The residual antegrade or collateral flow, and the volume and location of affected myocardium determine the characteristics of the clinical presentation. Patients with complete occlusion may manifest ST segment elevation MI, if the lesion occludes an artery supplying a substantial volume of the myocardium. A similar occlusion in the presence of extensive collaterals may present as MI without ST segment elevation. ST segment elevation MI is diagnosed by the presence of a clinical syndrome of new-onset ischemia with either rest pain or a crescendo pattern of ischemic pain on minimal exertion, and elevated enzymatic markers together with electrocardiographic evidence of acute ischemic injury. The predictive accuracy of ST segment elevation for a final diagnosis of MI is very high. The definition of MI proposed by the European Society of Cardiology (ESC)⁴, the American

113. Wolk R, Lusawa T, Ceremuzynski L. Effects of glucose-insulin-potassium infusion on QT dispersion in patients with acute myocardial infarction. *Ann Noninvasive Electrocardiol* 2001;6:50-54.
114. Rowe JW, Tobin JD, Rosa RM, Andres R. Effect of experimental potassium deficiency on glucose and insulin metabolism. *Metabolism* 1980;29:498-502.